REMARKS

Amendments to the Claims

Claims 1, 2 and 3 have been amended to clearly define the subject matter of the invention. Support for this amendment can be found throughout the Specification, for example, at page 9, lines 4-7, page 10, lines 15-24, page 60, lines 8-17; and Example X at page 80, lines 12-16. Additional support is found in the Specification of priority application U.S. Serial No. 07/670,827, filed on March 18, 1991, for example, at page 13, lines 5-8; page 18, lines 17-19; page 20, lines 3-6; and Example X at page 67, line 12 and page 68, line 25.

Claim 21 has been cancelled.

Claims 34-39 have been added to claim methods of inhibiting TNFα in a human patient having inflammation associated with amylotrophic lateral sclerosis (ALS). Support for these claims is found throughout the Specification. In particular, support for amylotrophic lateral sclerosis (ALS) is found in priority application U.S. Serial No. 08/013,413 on page 35, line 35. This application is incorporated by reference at page 1, lines 4-20 of the instant application. Claims 38-39 find support in Table 5, page 101 and Table 6, page 102 of the instant Specification. No new matter has been added. Therefore entry of these amendments is respectfully requested.

Amendments to the Specification

A preliminary amendment was filed October 3, 2006 that corrected the specification including trademarks and other inconsistencies objected to by the Examiner.

Accession No. Argument

Applicants submitted the proper Accession No. and related information in the Preliminary Amendment filed on October 3, 2006. Applicants respectfully request submittal of the comment. The text has been reproduced below.

"Applicants have amended the specification to recite "ATCC Accession No. PTA-7045," and to recite that c134A was deposited pursuant to the Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 22, 2005. Support for this amendment is found in the specification,

as amended, for example, at page 25, lines 15-22. In addition, support for reference to the cell line for the A2 antibody is found in the priority application U.S. Serial No. 07/670,827, filed March 18, 1991, at page 19, lines 14-20. Filed concurrently herewith is a Statement Under 37 C.F.R. §1.804, §1.806 and §1.808."

Priority

The Examiner states on page 2 of the Office Action dated January 3, 2007, that the instant application has the "priority date of USSN 08/013,413 filed 2/2/93, as this appears to be the first USSN in the priority chain for the instant application to disclose the treatment of neurodegenerative diseases, including the elected species ALS." Applicants respectfully disagree. As discussed below, the pending claims, particularly as amended, are entitled to claim the benefit of priority application USSN 07/670,827, filed March 18, 1991.

The priority application USSN 07/670,827 discloses at page 39, line 20 through page 40, line 9 that "the antibodies, fragments, and derivatives of the present invention are useful for treating a subject having a disease or condition associated with levels of a substance reactive with an anti-TNF antibody, in particular TNF, in excess of the levels found in a normal healthy subject. Such diseases include ... chronic inflammatory diseases...." Additionally, support for the use of anti-TNF antibodies to treat inflammation associated with chronic inflammatory disease is found in this priority application at page 3, lines 13 through 15, which discloses that "TNF is noted for its pro-inflammatory actions which result in tissue injury." Further support is found in this priority application at page 10, line 22 through page 11, line 4. Because this priority application teaches the treatment of TNFα-mediated inflammation by administration of anti-TNF antibodies and TNF pro-inflammation associated with chronic inflammatory diseases, the priority application discloses the method of treating inflammation associated with TNFα by administration of the claimed anti-TNFα antibodies. The claims have been amended to recite "inflammation associated with" neurodegenerative diseases. These neurodegenerative diseases are a subset of inflammatory diseases where the pro-inflammatory cytokine, TNFα, is implicated as a significant factor in causing inflammation. For these reasons, the claims, particularly as amended, are entitled to claim the benefit of priority application U.S. Serial No. 07/670,827, filed March 18, 1991.

Applicants submit that the priority of newly added Claims 34-39 enjoy the priority date of at least USSN 08.013,413 filed 2/2/93, as this appears to be the first application in the priority chain for the instant application to disclose the treatment of ALS.

Objection to the Abstract

The abstract was objected to for not adequately describing the claimed invention. As indicated above, the abstract has now been amended to more particularly describe the claimed invention. Support for this amendment is found throughout the Specification, in particular, on page 10, lines 15-24, page 16, lines 7-12 and page 57, line 25 to page 58, line 15. Withdrawal of the objection is respectfully requested.

Objection to the Specification Under 37 C.F.R. § 1.75 (d)(1) and M.P.E.P § 608.01(l)

The specification was objected to for failing to provide proper antecedent basis for recitation of paracetamol and dextroporoxyphene in Claims 15 and 16. Applicants direct the Examiner's attention to Table 5, page 101 and Table 6, page 102 of the instant Specification. Table 5 provides proper antecedent basis for paracetamol and Table 6 provides proper antecedent basis for dextroporoxyphene. Withdrawal and reconsideration of the objection are respectfully requested.

Rejection of Claims 1-7, 15-16 and 18-33 Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 15-16 and 18-33 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1-7, 15-16 and 18-33 are also rejected on the grounds that the specification does not contain a written description of the claimed invention.

With regard to enablement, the Examiner states that the cA2 antibody must be known and readily available to the public, or obtainable by a repeatable method set for in the specification, or else a deposit of the cell line/hybridoma may be made in order to satisfy the enablement requirement.

37 C.F.R. § 1.809 (b)(1) states that "[t]he applicant for patent or patent owner shall reply to the rejection under paragraph (a) of this section by (1) In the case of an applicant for patent, either making an acceptable original...deposit, or assuring the Office in writing that an acceptable deposit will be made...." In addition, 37 C.F.R. § 1.809 (d) states that "[f]or each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository."

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to expedite prosecution, and in accordance with 37 C.F.R. § 1.809 (b)(1), on September 22, 2005, Applicants deposited the cell line for the A2 antibody (designation c134A) with American Type Culture collection (ATCC) under the Budapest Treaty. The ATCC accession number is PTA-7045.

The specification at page 25, lines 15-22 has been amended to recite "As examples of antibodies according to the present invention, murine mAb A2 (ATCC Accession No. PTA-7045) of the present invention is produced by a cell line designated c134A." The specification at page 25, lines 16-23 has been further amended to recite "c134A was deposited pursuant to the Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 22, 2005."

Support for deposit of the cell line for the A2 antibody is found in the specification, for example, at page 25, lines 15-22. In addition, support is found in the priority application US Serial No. 07/670,827, filed March 18, 1991, at page 19, lines 14-20.

A Statement Under 37 C.F.R. §1.804, §1.806 and §1.808 was filed on October 3, 2006. Entry of this Statement is respectfully requested.

Rejection of Claims 1-7, 15-16 and 18-33 Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 15-16 and 18-33 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, on page 7 of the Office Action dated January 3, 2007, the

Examiner states that "*in vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species and model-dependent, it is not clear that reliance on the *in vitro* and *in vivo* experimental observation of the anti-inflammatory properties of "TNFα-specific antibodies accurately reflect the relative efficacy of the claimed therapeutic strategy to treat or 'inhibit the action of TNF for treating neurodegenerative diseases' with TNFα-specific antibodies."

Further, the Examiner states that "pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, *i.e.,* such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e., such as adverse side effects prohibitive to the use of such treatment."

In regard to the Examiner's statement regarding proteolytic inactivation, Applicants note that A2-specific monoclonal antibodies have long half-lives (for example, REMICADE® infliximab has a serum half-life of 9.5 days and still detectable in serum 8 weeks after infusion) (see Exhibit A, Cornillie *et al.*, "Infliximab Induces Potent Anti-inflammatory and Local Immunomodulatory Activity but no Systemic Immune Suppression in Patients with Crohn's Disease," *Aliment. Pharmacol. Ther., 15*: 463-473, at 463 (2001)). In fact, monoclonal antibodies by their nature have long half-lives. A2-specific monoclonal anti-TNFα antibodies are generally administered intravenously or subcutaneously. They are not subject to proteolytic degradation, which may occur with oral administration of certain proteins. In regard to the Examiner's statement regarding reaching the target area, Applicants note that the A2-specific antibodies do cross the mucosa as seen in clinical trials with Crohn's disease (see Exhibit A). Further, in regard to the Examiner's statement regarding suitability of A2-specific antibodies for *in vivo* therapeutic use, Applicants note that A2-specific antibodies, such as REMICADE® infliximab, have been used for over a decade to treat effectively other diseases associated with excess levels of TNF α such as Crohn's disease, establishing that these antibodies are safe and effective for *in vivo* therapeutic use (see Exhibit A).

Additionally, the Examiner questions the utility of macromolecules that minimally traverse administration and have negligible brain penetration, noting the document "New Therapeutic Strategies and Drug Candidates for Neurodegenerative Diseases" (Greig, *et al.*, *Ann. N.Y. Acad. Sci,* 1035:290-315 (2004)). Applicants respectfully disagree with the Examiner's assertion.

Applicants' elected invention is directed to methods for inhibiting the action of TNFα for treating inflammation associated with neurodegenerative diseases in a human. In certain embodiments, the methods further comprise a pain control agent. Further, newly added claims are directed to the treatment of inflammation associated with ALS. Applicants note that page 59, line 23 to page 63, line 24 of the Specification details various methods of administration of anti-TNFα antibodies. For example, on page 61, lines 18-25, the Specification details the therapeutic administration of anti-TNF peptides or antibodies with the use of a vehicle for delivery, including the use of liposomes. One skilled in the art upon studying the Specification would know how to make and use Applicants' invention for therapeutic administration to achieve the desired therapeutic effects.

Applicants have provided the Pardridge reference herein, (Exhibit B), that teaches strategies known in the art for delivery to the brain of antibodies and these strategies include (1) neurosurgery-based strategies; (2) pharmacology-based strategies for small molecules; and (3) physiology-based strategies. (See, *e.g.,* page 240, second column, lines 6-8). One skilled in the art would readily apply one of these strategies for delivery, for example the use of liposomes, with pharmacology-based strategies. As shown above, Applicants described this use of a liposome delivery system in the Application as filed.

Enclosed are two articles (Exhibit C and Exhibit D) showing that antibodies can cross the blood brain barrier (BBB). The reference (Exhibit C), by Bard *et al.,* describes direct evidence of labeled amyloid antibodies peripherally administered entering the central nervous system and binding to amyloid plaques located in the brain. Bard *et al.* states "These results indicate that antibodies can cross the blood-brain barrier to act directly in the central nervous system and should be considered as a therapeutic approach for the treatment of Alzheimer disease and other neurological disorders". (See Abstract, page 916, lines 22-26). Additionally, the reference by Brok *et al.* (Exhibit D) describes a labeled monoclonal antibody traversing the BBB and binding

to lesions on the brain, see Fig. 6, page 6561 and page 6557, second column, line 41 to page 6558, first column, line 9. Both references demonstrate the ability of an antibody to cross the BBB without a specialized transport system. In view of the above, Applicants have enabled one skilled in the art to make and use the invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner further states that "given the breadth of 'neurodegenerative diseases', the absence of working examples and the formidable challenge of treating neurodegenerative diseases with TNF-α-specific inhibitors, including the treating neurodegenerative diseases with the claimed TNF-α-specific antibodies, there appears to be insufficient guidance and direction as to how [sic] practice the breadth of treating 'neurodegenerative diseases' to be treated by administering 'a TNF-α inhibiting amount of an TNF-α antibody' to treat 'any neurodegenerative disease'." Applicants disagree with this assertion. As discussed above, the claims recite "inflammation associated with ." Further, as discussed in Exhibit A, TNFα antagonists, including the antibodies of the present invention, have been used safely and effectively to treat diseases associated with inflammation due to the pro-inflammatory cytokine, TNFα. Articles published after the filing date show that an invention was properly enabled when this evidence shows the state of knowledge in the art as of the filing date. *Gould v. Quigg*, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

Although TNFα expressed at normal levels may have some neuroprotective effect, it is known in the art that excess levels of TNFα lead to inflammation and tissue damage. TNFα is a pleiotropic regulatory cytokine that exerts effects on various members of regulatory pathways. The fact that there is a neuroprotective effect of TNFα is not dispositive that there can be no benefit from inhibiting the negative effects of TNFα on inflammation in the disease state. In fact, Applicants' disclosure provides ample examples of these benefits. One of skill in the art would know that inflammation associated with neurodegenerative diseases occurs in connection with the harmful over-production of TNFα, not with the protective effects of low levels of TNFα. Therefore, one of skill in the art would know how to determine when inflammation would be amenable to treatment with anti-TNFα antibodies.

The Examiner directs Applicants' attention to the teachings of Venters *et al.* (TINS 23: 175-180, 2000), noting that Venters asserts that observations of contrary findings concerning the

neurotoxic/neuroprotective properties of TNFα are acknowledged and that the exact factors responsible for shifting the roles of TNFα from neurotoxicity to neuroprotection are not known.

It is not surprising that TNFα, a pleitropic regulatory cytokine, may have different roles in the regulation of response to the cytokine. Further a more detailed review of the article suggests that the "antithetical roles of TNF-α in neurodegenation [sic] might be related to the dual nature of inflammation: the sequestration and elimination of tissue that is too damaged to repair, and the rescue of tissues that have escaped irreparable harm." Further, on page 179, top paragraph, the article states "[i]n the brain, overproduction of TNFα and other pro-inflammatory cytokines has been implicated in a variety of neuropathologies, including the AIDS-demential complex, stroke trauma, multiple sclerosis and Alzheimer's disease". Moreover, the article states that the emerging concept is that the clinical outcome of inflammatory events in the CNS is dependent of the balance between pro- and anti-inflammatory cytokines." TNFα and other cytokines are responsible for the body's response to inflammation. Thus, consistent with this teaching, treating the overproduction of TNFα with an anti-TNFα antibody, such as A2-specific antibodies, such as REMICADE® infliximab, would be beneficial in restoring the body back to homeostatis, balancing the conflicting roles.

The rejection also points to an article , Cytokines Role in Neurodegenerative Events by Viviani, *et al.* (Toxicology Letters, 149: 85-89, 2004) pointing out "controversy associated with the neurotoxic properties of the cytokine TNF-α, including the lack of causing neuronal death in healthy brain/neuronal tissues as well as indications of neuroprotective effects on TNF-α.... Here, the various parameters contributing to the circumstances combinatorial effects allowing a single cytokine to transmit diverse signals." While there is controversy regarding normal tissues, the article also points out the benefits of a TNFα antibody in damaged tissue. See page 86, column 1, last paragraph. The authors further suggest a study of micro-environment of the cells, See 86, column 2, paragraph 1. While there are conflicting studies regarding the involvement of TNFα in neurotoxic and neuroprotective activities, the use of an antibody to TNFα to treat disease states has been beneficial.

The Examiner also questions whether the application has sufficient direction and guidance as to how to choose which "neurodegenerative diseases" are amenable to treatment

with anti-TNF-α antibodies insinuating that the claims do not appear to take into account the broad diversity of diseases encompassed and targeted by the claimed invention.

Again this assertion is without merit for lack of evidence. Applicants have demonstrated the ability to inhibit the action of TNF-α in inflammation in a variety of diseases using with an anti-TNFα antibody or antigen-binding fragment thereof. In fact, the inhibition of TNFα using A2-specific antibodies, such as REMICADE® infliximab is beneficial to treatment of patients with a wide range of diseases having broad diversity. See for example, Exhibit A.

The Examiner considers the art to be unpredictable. Applicants respectfully disagree, however, even if this is true, the patent statutes do not require absolute predictability, only that it would not require undue experimentation to practice the claimed method. Applicants assert that practicing the claimed method does not require undue experimentation.

In view of the above, Applicants submit that the claims have sufficient written description and are enabled under 35 U.S.C § 112, first paragraph. Withdrawal and reconsideration of the rejection are respectfully requested.

Rejection of Claims 1-7, 15-16 and 18-33 Under 35 U.S.C. § 103(a)

Claims 1-7, 15-16 and 18-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Le *et al.* (WO 92/16553) in view of Beck *et al.* (*Acta Neurol. Scand.* 78:318-323, 1988) Chofflon *et al.* (*Eur. Cytokine Netw.* 3:523-531, 1992) and Selmaj *et al.* (*Ann Neurol.* 30: 694-700, 1991). Applicants respectfully disagree.

As noted above, the instant application's elected claims have priority to March 19, 1991. As such, the only reference cited that dates prior to this priority document is the Beck *et al.* reference. As noted by the Examiner, this reference teaches that TNF triggers exacerbation of clinical events in multiple sclerosis patients and this cytokine plays a role in maintaining disease in chronic progressive and invalidating forms. Further, Beck teaches that experimental mice with cerebral manifestations can be protected with anti-TNFα antibodies. However, Beck does not teach Applicants' claimed antibodies or methods.

Applicants note that the Examiner is relying on the other references to expand the teachings of Beck. See Office Action page 10. As these reference do not qualify as prior art,

reliance on the references for the obviousness rejection is improper. Reconsideration and withdrawal of the rejection are requested.

Rejection Under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 1-7, 15-16 and 18-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of U.S. Patent No. 6,991,791.

Applicants will address this matter in regard to the pending claims upon indication of allowable claims.

Rejection Under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 1-7, 15-16 and 18-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 4, 5, 7-10, 12, 14, 21, 23 - 24, 30, 35, 37 and 52-58 of copending USSN 10/227,488. Applicants will address this matter in regard to the pending claims upon indication of allowable claims in either application as this is a provisional rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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